# Glomerular volume and renal histology in obese and non-obese living kidney donors

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**The link between obesity and renal disease is unclear, and there is no consensus as to whether obese individuals are at increased risk for kidney disease after living kidney donation if they otherwise meet acceptance criteria. We retrospectively studied time-zero (implantation) biopsies in 49 obese (body mass index (BMI) $\geqslant 30\,kg/m^2$) and 41 non-obese (BMI $< 30\,kg/m^2$) renal donors that met acceptance criteria. We found that our obese donor population had higher systolic blood pressure ($P < 0.001$ vs non-obese) and higher absolute iothalamate clearance ($P = 0.001$ vs non-obese) before donation. The obese donors had larger glomerular planar surface area compared to non-obese controls ($P = 0.017$), and this parameter correlated with patient weight and urinary microalbumin excretion. Detailed examination of the biopsies revealed that although most histologic findings were similar between groups, the obese donors had more tubular dilation ($P = 0.01$), but less tubular vacuolization ($P = 0.02$) than the non-obese controls. There was also a trend toward more arterial hyalinosis in the obese patients than controls ($P = 0.08$). From these data, our studies detected subtle differences in donor organs obtained from obese compared to non-obese individuals. Further studies should be carried out to quantify the long-term impact of these findings.**

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Reports examining 10- and 20-year outcomes of living kidney donors selected for normal weight and in excellent health support the general safety of living kidney donation.[1] However, the increasing shortage of deceased donor kidneys and practical advantages associated with living donor kidney transplants have led to wider consideration of living donors previously considered too old, too heavy, or excluded owing to elevated blood pressures. Obesity in kidney donors is controversial because of the potential for both short- and long-term complications. Pressures to examine this question are rising as a result of rapidly increasing body weight over the past decade in most Western populations. The long-term risk of living with a solitary kidney is unknown for obese donors. This group appears intuitively to be at increased risk for the development of obesity-related comorbidities such as diabetes, which may affect long-term renal function of the donor. We recently reported that the perioperative complication rate and short-term renal function of obese donors is similar to that of non-obese donors using current methods of laparoscopic nephrectomy.[2]

We examined whether individuals without evident functional abnormalities (reduced glomerular filtration rate or proteinuria) who chose to donate a kidney may nonetheless harbor undetected renal abnormalities. We hypothesized that obesity might stimulate renal hypertrophy leading to acceptable levels of glomerular filtration despite the presence of occult renal disease. The aim of this study was to examine the possibility of unrecognized pathologic changes in both non-obese (body mass index (BMI) $< 30\,kg/m^2$) and obese (BMI $\geqslant 30\,kg/m^2$) donors at the time of living donor nephrectomy using detailed histologic and morphometric analysis of baseline (implantation) allograft biopsies. We report results of a series of obese and non-obese donors undergoing donor nephrectomy between January 2000 and March 2003.

## RESULTS

Our study population consisted of 41 non-obese donors (BMI $< 30\,kg/m^2$) and 49 obese donors (BMI $\geqslant 30\,kg/m^2$) who donated kidneys to a spouse, relative, or friend. The demographics for these groups are shown in Table 1. Both groups had similar mean ages and similar distribution of male and female subjects. The two groups of donors had

**Table 1 | Demographics and laboratory values in living kidney donors**

| Variable[a] | Non-obese (*N*=41) | Obese (*N*=49) |
|---|---|---|
| Age (years) | 40±9 (19–58) | 43±11 (19–67) |
| Gender (male:female) | 15:26 | 20:29 |
| Donor height (m) | 1.70±0.10 (1.49–1.87) | 1.67±0.08 (1.42–1.89) |
| Donor weight (kg) | 72.2±11.8 (50.8–95.3) | 105.2±17.6 (73.0–162.7) |
| Donor BMI (kg/m$^2$) | 24.8±2.2 (20.5–28.7) | 37.6±5.0 (30.3–59.0) |
| Pre-donation serum Cr (mg/dl) | 1.2±0.2 (0.8–1.4) | 1.0±0.1 (0.8–1.4) |
| Pre-donation urine Microalbumin (mg/24 h) | 7.9±7.9 (2.0–41.0) | 8.4±5.1 (1.0–25.0) |
| Pre-donation systolic blood Pressure (mm Hg)[b,*] | 123±13 (100–153) | 136±15 (110–176) |
| Pre-donation diastolic blood Pressure (mm Hg)[b,**] | 73±9 (53–94) | 77±10 (54–106) |

Abbreviations: BMI, body mass index; Cr, creatinine.
[a]Mean±s.d. (range), except where noted.
[b]Blood pressure readings were at the initial evaluation, see text for details.
*$P<0.001$ (obese vs non-obese).
**$P=0.06$ (obese vs non-obese).

similar height; however, as expected, there was a significant difference in the groups as to their weight, and consequently BMI. The pre-nephrectomy serum creatinine level was not different between the non-obese and obese donors, with the mean values being 1.2±0.2 and 1.0±0.1 mg/dl, respectively. Microalbumin measured on 24 h urine collection was also not different between the groups. The mean pre-donation systolic blood pressure was higher in the obese donors than in the non-obese donors (136±15 vs 123±13 mm Hg, $P<0.001$), and there was a similar trend in diastolic blood pressure with higher readings in obese donors (77±10 vs 73±9 mm Hg, $P=0.06$).

The pre-donation renal function for the two groups is shown in Figure 1. The left half of the figure shows the absolute value of iothalamate clearance (ml/min) as median, lower and upper quartile, and range. As a group, these values were higher in the obese donors than the non-obese donors ($P=0.001$). When adjusted for body surface area ('corrected' iothalamate clearance (ml/min/1.73 m$^2$)), there was no difference between the two groups ($P=0.72$).

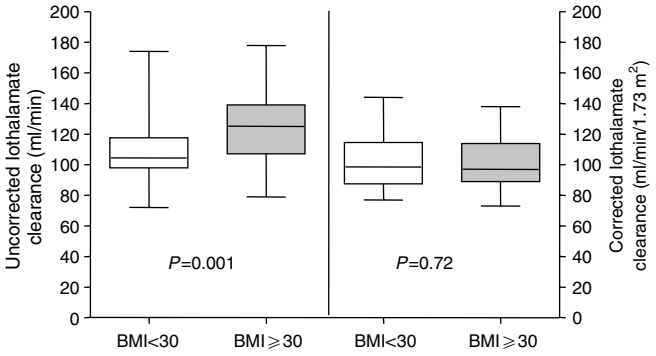


**Figure 1 | Pre-donation iothalamate clearance**. The median, 25th and 75th percentile values, and range are shown for the uncorrected (left, in ml/min) and corrected iothalamate (right, in ml/min/1.73 m$^2$) clearances for the non-obese ($N=41$, BMI<30 kg/m$^2$) and obese ($N=49$, BMI⩾30 kg/m$^2$) living kidney donors. There was a statistically significant difference in the uncorrected values between the non-obese and obese donors ($P=0.001$); this difference disappeared when standardized for body surface area ($P=0.72$).

Figure 2a–c show the scores assigned to the various histologic features observed in time-zero biopsies obtained from obese (BMI⩾30 kg/m$^2$) and non-obese (BMI<30 kg/m$^2$) donors. The scores for intimal arteritis (v), tubulitis (t), interstitial inflammation (i), and glomerulitis (g) are not shown and, not surprisingly, the vast majority received scores of '0', and there were no significant differences between the two groups. Shown in Figure 2a are the scores assigned to glomerulopathy (cg), intimal thickening (cv), tubular atrophy (ct), and interstitial fibrosis (ci) components of the obese and non-obese donor's time-zero biopsies. Only 9.8% of donors had any fibrosis at baseline (all grade 1). Atrophy of isolated tubules was common at time zero in both groups of donors, occurring in 59.2% of obese donors (all grade 1) and 53.6% of non-obese donors (all grade 1 expect one patient). Intimal thickening was not uncommon on these biopsies as well, 44.9% of obese donors had some intimal thickening (all grade 1 except in four individuals with grade 2) compared with 43.9% of non-obese donors (all grade 1 except in two individuals with grade 2). Despite these histologic findings, there were no differences in the distribution of scores between the obese and non-obese donors.

Other biopsy scores are shown in Figure 2b and c. There was no mesangial matrix (mm) increase seen in either the obese or non-obese donors. There was a greater incidence of mild arterial hyalinosis noted in the obese donor biopsies compared to the non-obese donor biopsies (44.9 vs 29.3% (all grade 1), $P=0.08$).Those donors with arterial hyalinosis did not have a different systolic or diastolic blood pressure when compared to donors without arterial hyalinosis ($P=0.30$ and 0.17, respectively). The incidence of tubular vacuolization was higher in the non-obese donors compared with the obese donors (68.3 vs 36.7% (all grade 1), $P=0.01$). These changes were predominately noted in the distal tubules. Conversely, the incidence of tubular dilation was higher in the obese donors than the non-obese donors (44.9 vs 22.0%, all grade 1, $P=0.02$). The scores for segmental sclerosis ($P=0.32$), tubular casts ($P=0.43$), interstitial edema ($P=0.42$), and endothelial cell swelling ($P=0.32$) did not differ between the groups. There was an increase in

glomerular hypertrophy in obese patients that approached statistical significance ($P=0.06$). When we tabulated the percentage of glomeruli that were globally sclerotic, the median (range) was 0.0% (0.0–20.0%) for the non-obese donors and 3.0% (0.0–17.6%) for the obese donors ($P=0.58$). By light microscopy, the estimated cortical fibrosis (%) was not different between the groups (non-obese vs obese, $3\pm1$ vs $3\pm1\%$, $P=0.28$).

In addition to general histologic changes, we specifically determined glomerular size in both groups of biopsies. Of the 90 donors selected for this study, 10 did not have glomeruli suitable for measuring the glomerular planar surface area (GPSA) owing to lack of a clear vascular pole. This left 80 donors with GPSA data available ($N=38$ with BMI $<30\,kg/m^2$ and $N=42$ with BMI $\geqslant 30\,kg/m^2$). The number of glomeruli (mean $\pm$ s.d. (range)) measured in the non-obese group was $17\pm8$ (3–37) compared to $21\pm13$ (1–43) in the obese group ($P=0.08$). Figure 3 compares the median, lower/upper quartile, and range of GPSA for the non-obese and obese donors. The mean GPSA was significantly greater in obese donors compared to non-obese donors (23 604 vs 20 878 $\mu m^2$, $P=0.017$).

There was a correlation between donor weight and GPSA (Figure 4a, Pearson $r=0.25$, $P=0.023$), and a correlation of the log (microalbumin) with GPSA (Figure 4b, Pearson $r=0.34$, $P=0.003$). The correlation between the mean GPSA and donor BMI also approached statistical significance (data not shown, Pearson $r=0.20$, $P=0.08$). There was no correlation between the uncorrected iothalamate clearance and mean GPSA (Pearson $r=0.16$, $P=0.18$), or the corrected iothalamate clearance and mean GPSA (Pearson $r=-0.02$, $P=0.84$).

The median follow-up after donation was 340 days (range 21–963 days). At this time, the serum creatinine was $1.3\pm0.2$ mg/dl ($N=60$ donors), and the serum creatinine in non-obese donors was similar to that in the obese donors ($1.4\pm0.2$ vs $1.3\pm0.2$, $P=0.83$). The uncorrected iothalamate clearance was $80\pm19$ ml/min and the corrected iothalamate clearance $69\pm14$ ml/min/1.73 $m^2$ ($N=44$ donors). The uncorrected iothalmate clearance was significantly lower in the non-obese patients compared to the obese ($71\pm15$ vs $87\pm19$, $P=0.004$), and the corrected values at follow-up were lower in the non-obese donors compared with the obese group ($65\pm12$ vs $72\pm15$, $P=0.05$). Follow-up microalbumin excretion was only available in 36 donors, and was

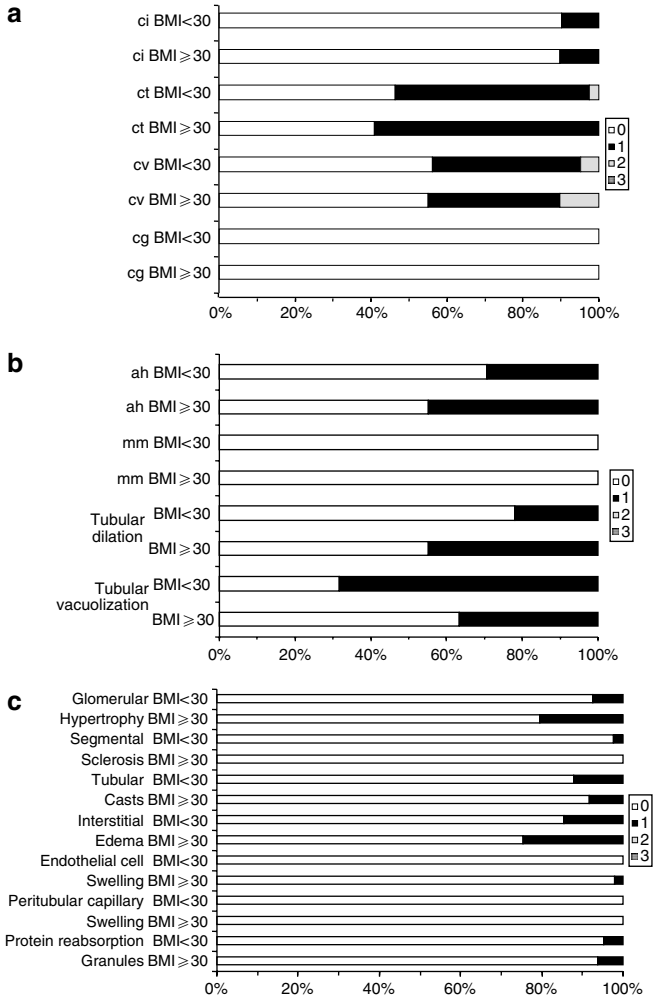


**Figure 2 | Histology scores for renal biopsies.** (**a**) Banff '97 chronic scores in non-obese and obese donors. The distribution of chronic Banff 97 scores for the time-zero biopsies in non-obese and obese donors is shown. The scores are shown as percentage of the total number of kidney donors ($N=41$ non-obese and $N=49$ obese) (cg, glomerulopathy; cv, fibrous intimal thickening; ct, tubular atrophy; ci, interstitial fibrosis). (**b**) Other time-zero biopsy scores in non-obese and obese donors. The distribution of other biopsy scores for the time-zero biopsies in non-obese and obese donors is shown. The scores are shown as percentage of the total number of kidney donors ($N=41$ non-obese and $N=49$ obese). There are significant differences in the scores for tubular vacuolization ($P=0.01$) and tubular dilation ($P=0.02$) between the groups. (mm, mesangial matrix increase; ah, arterial hyalinosis). (**c**) Time-zero biopsy scores in non-obese and obese donors (continued). The distribution of other biopsy scores for the time-zero biopsies in non-obese and obese patients is shown. The scores are shown as percentage of the total number of patients, $N=41$ non-obese and $N=49$ obese kidney donors. There are no significant differences between these groups (see text for details).

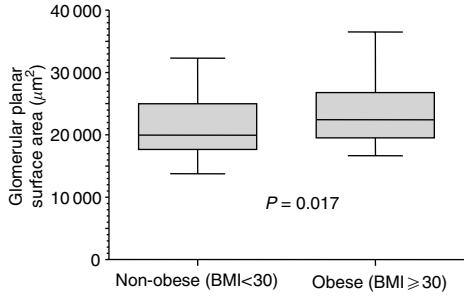


**Figure 3 | GPSA – non-obese vs obese donors**. The median, 25th, and 75th percentile values, and range are shown for GPSA ($\mu m^2$) for non-obese ($N=42$) and obese ($N=39$) kidney donors. The difference between these groups is statistically significant (mean (non-obese vs obese) 20 878 vs 23 604 $\mu m^2$, $P=0.017$).

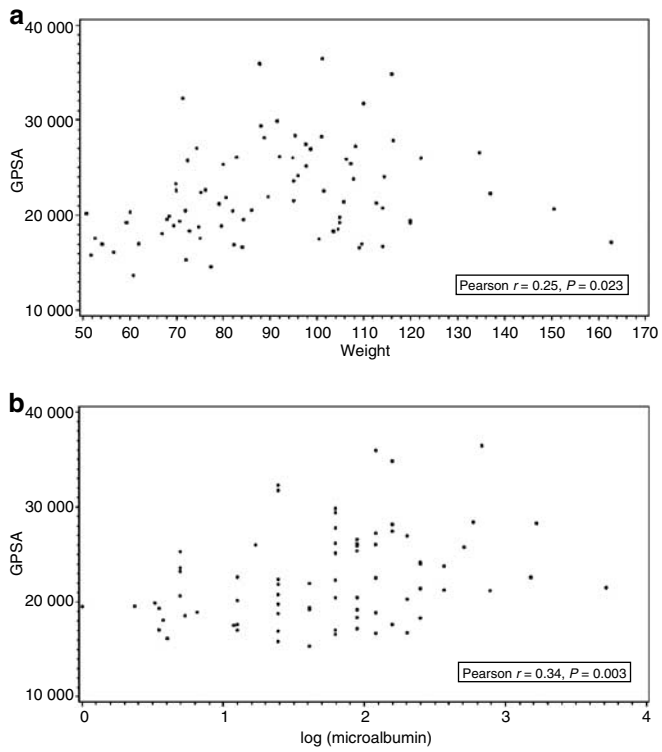


**Figure 4 | GPSA correlations.** (**a**) GPSA as a function of body weight. The correlation between GPSA ($\mu m^2$) and patient weight (kg) is shown. A weak but significant relationship was noted (Pearson $r = 0.25$, $P = 0.023$) between these variables. As discussed in the text, GPSA did not correlate with BMI (kg/m$^2$). (**b**) GPSA as a function of log (microalbumin). The correlation between the log of the pre-donation microalbumin excretion and BMI is shown. There was a good correlation of these two variables (Pearson $r = 0.34$, $P = 0.003$). GPSA was correlated with the left censored microalbumin values using the method of Lynn.[18]

$9 \pm 10$ mg/24 h with no difference between the non-obese and obese donors ($11 \pm 15$ vs $8 \pm 4$ mg/24 h, $P = 0.24$).

## DISCUSSION

A major purpose of the living donor kidney evaluation is to exclude clinical kidney disease. The relationship between functional studies and histopathologic features in otherwise healthy obese individuals is not well established. One potential value of examining biopsy material is to provide a basis for anticipating the long-term impact of donor nephrectomy. The current study failed to demonstrate occult renal disease such as glomerulopathy on time-zero biopsies in any of the obese donors who met our selection criteria. However, these results did demonstrate subtle pathologic changes that were more pronounced in obese donors. These pathologic changes were found in donors with normal albumin secretion and normal renal function.

The significance of these pathologic changes is unknown. We found no differences in glomerulopathy (cg), intimal thickening (cv), tubular atrophy (ct), and interstitial fibrosis (ci) scores for these two groups. Our group has previously reported that baseline mild fibrosis and tubular atrophy is present in a small percentage of living donor kidneys.[3] We detected an increase in the prevalence of mild hyalinosis in the time-zero biopsies of obese donors compared to non-obese donors. Although the cause and significance of mild hyaline deposition in kidneys is not known, hyalinosis has been associated with hypertension and increased age. It should be noted that we analyzed only initial blood pressure readings here; all donors with elevated readings underwent further testing using 18 h ambulatory blood pressure monitoring before acceptance (data not shown). However, we did not demonstrate more hyalinosis in donors with elevated systolic blood pressure. The finding that a third of non-obese donor kidneys demonstrated hyalinosis supports a cause owing to factors other than obesity. Morphometric vascular dimensional analysis of implantation biopsies from a different donor cohort suggests that thickening of vascular wall layers is related mainly to donor age.[4]

The significance of increased tubular dilation in obese donor biopsies and the increase in tubular vacuolization in the non-obese donor biopsies is unclear. To our knowledge, these pathologic findings have not been systematically studied in renal biopsies. We can only speculate on the etiology of these changes and are currently examining them further in a larger, retrospective study of transplant biopsies at our institution. Clearly, despite a rigorous selection protocol utilizing age-specific cutoffs for measured iothalamate clearance and urinary microalbumin excretion, we do find time-zero biopsies with pathologic changes; but the impact of these findings requires further study across a large population of donors. We recommend the systematic evaluation of time-zero biopsies by all institutions as a marker for donor selection and as a variable in the analysis of transplant outcomes.

Obese donors had greater mean GPSA in our study. Assuming that this translates into larger mean glomerular volume, these results confirm that larger body mass was associated with larger glomeruli in humans. GPSA measurements did not correlate with BMI or glomerular filtration rate but did correlate with donor weight and urinary microalbumin secretion. Numerous studies have shown that urine microalbumin is a predictor for future renal disease and mortality in diabetics, hypertensives, and the general population.[5–7] Formal morphometric assessment of the thickness of the glomerular basement membrane and the mesangial fractional volume – two measurements that may be associated with early glomerular disease were not performed in our study.[8] Whether increased microalbuminuria in a renal donor portends a shorter life of the transplanted kidney or poor function cannot be ascertained from our current study, which was restricted to donors with normal urinary microalbumin excretion. Whether donors who have elevated urinary microalbumin secretion should be allowed to donate due to a potential risk for increased cardiovascular morbidity is not known.

Although obesity increases the risk for later development of conditions such as diabetes and hypertension, which may in turn affect renal function, the impact of obesity alone on the development of renal disease remains poorly defined.[9] The earliest lesions associated with obesity-related glomerulopathy (ORG) have not been identified. ORG was noted by Weisinger *et al.*[10] in association with focal segmental glomerulosclerosis and nephrotic range proteinuria in massively obese patients. Although the prevalence and long-term clinical significance of this lesion remains poorly defined, a series reported by Kambham *et al.*[11] notes an increased incidence of this lesion in 0.2% of all biopsies received during 1986–1990 rising to 2.0% of biopsies received during the period of 1996–2000. When compared to a matched series of patients with focal segmental glomerulosclerosis at a mean follow-up of 27 months, patients with ORG were less likely to have nephrotic range proteinuria, less likely to double their creatinine, or progress to end-stage renal disease. Histologic findings of ORG noted in this series included increased glomerular size when compared to age- and gender-matched controls (measured by diameter) in association with more severe arteriolosclerosis, but fewer sclerotic glomeruli and less effacement of foot processes when compared to control patients with focal segmental glomerulosclerosis. The important difference is that the biopsies in our series came from donors who had excellent renal function and normal microalbumin excretion, whereas the biopsies reviewed in Kambham's series were performed owing to clinical evidence of renal dysfunction. The mean age in our series was higher, so it is unlikely that our subjects were accepted before the development of either proteinuria or sclerosis.

Two important questions posed by our current study are whether glomerulomegaly without sclerosis seen in the obese donor portends future renal dysfunction and whether unilateral nephrectomy has any impact upon this process. The impact of nephrectomy on the development of ORG or any other type of renal pathology in the remaining kidney, regardless of glomerular size at baseline, is unknown. There are no reported biopsy series in donors with larger glomeruli following nephrectomy. Long-term studies on donor outcomes do suggest a very low incidence of renal dysfunction. However, Praga *et al.*[12] have reported an increased incidence of proteinuria and renal insufficiency developing many years later in obese patients undergoing nephrectomy for non-malignant disease when compared to non-obese patients. It is unclear whether these findings apply to our donor population.

Whole kidney renal mass and specific renal dimensions were not measured in our study and measurement of the glomerular number per kidney was also not possible in these specimens. It could be hypothesized that the relative hyperfiltration of obese donor kidneys (increased iothalamate clearance) may stem from a relative deficit of renal mass and nephrons. It has been suggested that 'nephron dosing' may play a pathogenic role in the development of hypertension and progression of renal damage.[13] It may be that hyperfiltration in our obese donors precedes the development of an eventual renal injury (as in stage I diabetic nephropathy), and this may serve as a predictor of poor long-term outcome. Future areas of investigation should focus on long-term follow-up of obese donors to determine if increased glomerular size will impact renal function. In addition, morphometric and histologic analysis of allograft biopsies obtained serially following transplantation from donors with glomerulomegaly may be useful to further elucidate the significance of these lesions. Decreased allograft function in recipients with a time-zero biopsy demonstrating increased glomerular size has been reported, although donor weight was not investigated and the majority of the kidneys came from deceased donors.[14]

Although the current epidemic of obesity has negative effects on long-term health of those affected, risk to the potential obese donor who is otherwise in excellent health remains unclear. As would be predicted by normal preoperative evaluation of renal function, there were no donors with evidence of even mild glomerulopathy. However, obese donors did have an increased glomerular filtration rate, an increased prevalence of mild hyalinosis and tubular dilation, and increased glomerular size compared to non-obese donors. Although the advent of the laparoscopic technique has made donor nephrectomy safe and technically feasible in obese individuals, careful preoperative evaluation and continued donor follow-up will be necessary to determine the long-term impact of donor nephrectomy on obese living kidney donors.

## MATERIALS AND METHODS

This study was carried out with informed consent using a protocol approved by the Mayo Foundation Institutional Review Board. Potential living donors were evaluated according to accepted donor guidelines as part of the Mayo Clinic, Rochester Kidney/Pancreas transplant program, which included a thorough history study, physical examination, and laboratory evaluation as previously described.[15] Specific acceptance criteria during this period included limiting microalbumin excretion to less than 30 mg/day and fasting blood glucose levels to less than 110 mg/dl. Blood pressure evaluation included ambulatory BP monitoring.[16] Obesity was not considered an absolute contraindication, although patients were encouraged to lose weight before donation and to maintain a weight-loss program after donation. During the time period of this study, approximately 38% of accepted living donors were obese. Proteinuria or microalbuminuria was the main reason for denial in 11% of obese individuals not approved for donation compared to 7% of non-obese (BMI $< 30\,kg/m^2$) denied donor candidates. After donation, follow-up examinations at our institution were encouraged but not required; as available, we did extract serum creatinine, iothalamate clearance rates, and 24 h microalbumin excretion from the most recent data in the medical record.

For this study, we selected obese kidney donors from a prospectively maintained database of all donor/recipient renal transplant pairs performed at our institution. The database was also queried to retrieve non-obese donors of the same gender and similar age to the obese donors, in order to control for these effects

in the pathologic analysis. We selected only kidney donors where the recipient had undergone a time-zero protocol biopsy as part of our comprehensive follow-up. The time-zero (implantation) biopsy is performed after the completion of the vascular and ureteral anastomoses during the recipient surgery (approximately 30 min after reperfusion). Two 18-gauge core needle biopsies are obtained using an automated biopsy gun.

The time-zero biopsies were reviewed in a blinded fashion by a pathologist with extensive experience in renal biopsy interpretation. The biopsies were permanently fixed in paraformaldehyde and examined using hematoxylin and eosin, periodic-acid Schiff, and trichrome-stained sections. Routine immunohistochemistry and electron microscopy were not performed. These biopsies were scored using the 10 standardized Banff 97 criteria and the following additional criteria: glomerular hypertrophy, segmental or global glomerular sclerosis, tubular dilatation, tubular vacuolization, tubular casts, interstitial edema, and endothelial cell swelling.[17] All additional criteria were scored in a similar fashion to the Banff 97 pathologic classification, namely on a 0, 1, 2, 3 scale – reflecting none, mild, moderate, and severe changes. Additionally, the percentage of renal cortical surface area with fibrosis was estimated by the pathologist.

Morphometric analysis of glomerular size was performed in a blinded fashion by a single investigator. The periodic acid-Schiff stained slides (two per case) were examined and all glomeruli exhibiting a clear vascular pole were electronically captured as a JPG file at $\times 400$ using MetaVue™ software (v5.0). At a later session, the glomeruli were outlined using the same software and the resulting GPSA was converted from arbitrary square pixels into square microns ($\mu m^2$) using a calibrated standard. The mean and standard deviation were calculated for each donor. Based on repeated measurements of the glomeruli, the reproducibility of the GPSA measurements was within 5%.

SAS software (version 8.0, SAS Institute, Cary, NC, USA) was used for the statistical analyses. All continuous variables are reported as the mean $\pm$ s.d. Comparisons between the groups were performed using the Student's *t*-test with the Satterthwaite correction. Correlations for most variables were performed using Pearson's method. The data for microalbumin are left-censored (e.g. the values fall below a level of detection that varied over time) and correlations were made using the method of Lynn.[18] All *P*-values of less than 0.05 are considered statistically significant.

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